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Sweat chloride concentrations are higher in IRT-positive newborns with one CFTR mutation than in other IRT-positive neonates

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A neonatal screening program for CF has been carried out since 1991 by the CF Center of Florence on all the newborns of Tuscany, Italy, using a IRT/Lactase/IRT protocol.
From Feb. 20, 2001 to May 20, 2003, all the blood spots of children who resulted IRT-positive were tested for CFTR mutations (32 mutations, PCR OLA assay and DGGE analysis).
Aim: to investigate if difference exists in sweat chloride concentrations between non-CF neonates who were IRT-positive and carriers of a CFTR mutation, and those who were IRT-positive and negative to the genetic test.
During the period, 64,114 newborns were screened for CF and 744 resulted IRT-positive and were not affected by CF. Among them, 48 (6.4%) resulted carriers of a CFTR mutation (DF508 carriers n= 32, 66.6%). Of 744 non-CF, IRT-positive children, according to the screening protocol 161 underwent a sweat test (Gibson & Cook).
The minimum quantity of sweat collected was 60 mg (sweat rate 1.05 g/m2/min); the mean age at sweat test was 65 days, SD 42. Of these 161 neonates, 26 (16.1%) resulted to be carriers of a CFTR mutation (DF508 carriers n=18) and 135 were negative to genetic testing.
The mean sweat chloride concentration of CFTR mutation carriers was 16.4 mEq/L, SD 8.1 (median 14, range 8-41), whereas that of newborns negative to genetic test was 13.5 mEq/L, SD 5.1 (median 13, range 4-34) p=0.02, difference 2.9 mEq/L, CI95%: 0.5-5.2.
In our population we found a statistically significant difference between the mean sweat chloride concentration of non-CF, IRT-positive newborns with a CFTR mutation and that of those negative to genetic test.
These findings might be interpreted as a possible result of the mutated CFTR protein action on the sweat chloride concentration in the carrier newborns.
Telethon Italy, Grant EC1208/2000

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Diagnosis CF?: Functional chloride secretion, complete *CFTR* screening, sequencing and transcript analysis in patients with inconclusive sweat test and *CFTR* mutation screening

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Exclusion of mild or monosymptomatic CF often is difficult in condition of inconclusive sweat test and *CFTR* mutation screening. Functional analysis of CFTR chloride secretion by both nasal potential difference (nPD) and intestinal current measurement (ICM) has been proven to be of high sensitivity and specificity. This study aimed to correlate these methods with an extended genetic analysis in a preselected patient cohort with borderline diagnostic features, and to establish a most informative procedure.
From n=164 patients with mild CF phenotype, inconclusive sweat test and/or *CFTR* mutation screening, n=115 were investigated by ICM and n=49 by both nPD and ICM. Individuals with borderline/pathological sweat chloride or low normal/pathological chloride secretory responses (n=30) were included into extended genetic evaluation (complete *CFTR* mutation screening exon 1-27/intron 11+19 by SSCP-HD analysis, sequencing and transcript analysis).
In n=7 patients the results of ICM and/or nPD were CF-typical. No correlation with absolute sweat chloride concentrations was seen. Electrophysiological result interpretation was confirmed by the extended genetic investigation, revealing two pathogenic *CFTR* mutations only in the patients classified as CF upon ICM/nPD.
Chloride secretory phenotypes were consistent with the extended genetic analysis in this highly informative patient cohort. ICM/nPD evaluation of patients with borderline phenotype aids in the diagnostic process and should be applied in cases of inconclusive routine tests.

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Congenital bilateral absence of the vas deferens (CBAVD): when does it lead to cystic fibrosis (CF) diagnosis?

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Introduction: male infertility, particularly CBAVD is a typical finding in classical CF. Atypical CF may presents as isolated CBAVD in patients (pts) with two CF mutations and positive or border line sweat test. CFTR dysfunction is often associated with the etiopathogenesis of CBAVD. Aim of this study is to investigate the relationship between CBAVD and CF diagnosis. *Methods*: 13 pts with CBAVD and one/two CFTR mutations or polymorphism were referred to our CF center. *Results*: mean age was 32.5 yrs, min-max 26-39; clinical history was not relevant in all but 5 pts (respiratory symptoms). 8/13 pts had been smokers in their life. Genetic assessment showed: a severe plus a mild mutation in 8/13 cases, a severe mutation plus poli-T 5/7 or 5/9 polymorphism in 4 pts and poli-T 5/9 alone in one pt. Sweat test (Cl mean value 69.9 mEq/l, min-max 46.2-101) was positive in 9 pts, border line in 4 pts. Mean FEV1was 99.4%, min-max 84-116. Chest X-ray demonstrated bronchial markings in 9/13 pts, was normal in 4/13 pts. Sputum culture was positive for Pseudomonas aeruginosa in 4/13 pts, Stenotrophomonas maltophilia in 1 pt, Staphilococcus aureus in 1 pt, negative in 7 pts. Mean BMI was 24.3 min-max 20-30. Sinusopathy was demonstrated in 8/13 pts, no other CF-related disease was detected at diagnosis. In *conclusion* a classical form of CF was confirmed in 4 pts, in 7 pts a diagnosis of atypical CF was performed and CF was temporarily excluded in 2 pts. No pt presented a relevant respiratory disease despite individual findings of infection, chest X-ray, anamnestic data. The prognosis of these pts is not foreseeable and they need to be monitored for the development of CF complications; treatment needs to be individualized.

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p.S1235R : a cystic fibrosis causing or non-causing mutation? Results from a French Molecular collaborative study

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More than 1300 different mutations in the CFTR gene, causing or non-causing disease, have been reported to the CF Consortium. p.S1235R, initially reported in a CF patient with a second mutation on the same allele (p.G628R), has been found at a frequency higher than that of many other mutations and its clinical significance is not clear.
The aim of this study is to compare the phenotypes of 57 subjects with p.S1235R in order to classify this sequence anomaly. They were referred for diagnosis of classical CF, non-classic or atypical phenotypes or carrier screening. The entire coding and flanking regions and six microsatellite markers were analyzed. 8 patients (3 CF, 4 CBAVD, 1 ICP) and 2 normal individuals were compound heterozygotes for a severe CFTR mutation. p.S1235R was found to be associated on the same allele with a stop mutation (p.R785X) in 2 CF patients with a severe disease and TG13-T5 in the 4 CBAVD patients. The CF patient with a mild phenotype, the ICP patient and the normal subjects did not carry a complex allele.
Our data suggest that another CFTR mutation may influence the pathogenic effect of p.S1235R in severe classical CF or in patients showing pathology closely linked to mutations in the CFTR gene. However, p.S1235R alone, when combined in *trans* with a second CF mutation, may be associated with a mild phenotype or with absence of clinical manifestations.